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Septic Shock: On the Importance of Being Tolerant

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A study by Figueiredo et al. (2013) in this issue of *Immunity* demonstrates that administration of anthracyclines induces autophagy in vivo and has a powerful protective effect in a mouse model of sepsis.

Septic shock remains one of the most formidable problems in critical-care medicine (Rittirsch et al., 2008). It is typically caused by bacteremia and the ensuing systemic inflammatory response to infection. Some patients can gradually recover and survive the ordeal. Sadly, many reach a tipping point whereupon they sink into an ultimately lethal downward spiral of cascading failures of multiple tissues and organs. An early aggressive antibiotic treatment to control the infection is essential but often insufficient to prevent a lethal outcome. The mortality rate depends on the timing of antibiotic administration, but other than that, it is not entirely clear why some patients manage to recover while others get tipped over the edge and quickly become impossible to save. Needless to say, the puzzle of septic shock has haunted clinicians and basic scientists for decades as efficient therapies for this deadly condition have remained unavailable (Iskander et al., 2013). A study by Moita and colleagues in this issue of *Immunity* describes an unexpected and powerful therapeutic effect of anthracyclines in a mouse model of polymicrobial sepsis.

In this study, Figueiredo et al. used a chemical screen to identify compounds with anti-inflammatory properties. Among the inhibitors they identified are epirubicin, doxorubicin, and daunorubicin, the anthracycline family drugs used for chemotherapy of several cancers. Anthracyclines cause DNA damage by intercalating between base pairs and by inhibiting topoisomerase II, the enzyme involved in relaxing supercoiled DNA (Minotti et al., 2004). These effects result in inhibition of DNA replication, cell-cycle arrest, and apoptosis of proliferating cells. Figueiredo et al. used a cecal ligation and puncture (CLP) model of sepsis to test the effect of anthracyclines on bacteremia and sepsis progression. Surprisingly, they found that anthracycline administration at the time of the CLP procedure dramatically improved the survival of mice without affecting bacterial burden. This indicated that anthracyclines promoted organ protection from sepsis, a conclusion supported by the reduction of several markers of organ damage in anthracycline - treated mice. As expected, administration of a broad spectrum antibiotic (meropenem) resulted in a strong reduction of bacterial burden, but although this delayed CLP-induced mortality, it did not prevent it. Importantly, both epirubicin (anthracycline) and meropenem (antibiotic) administration suppressed production of inflammatory cytokines, including interleukin-1, tumor necrosis factor, and high-mobility group box 1. This indicated that reduced cytokine production observed in epirubicin-treated mice is not sufficient to prevent mortality, suggesting that the effects of anthracyclines cannot be entirely explained by their anti-inflammatory properties and that they might work by promoting tissue protection from inflammatory damage.

These findings illustrate the distinct contribution of tissue protection in host defense against infection. Resistance and tolerance are two strategies the host can use to survive an infection—the former reduces pathogen burden, and the latter minimizes damage caused by a given level of infection without directly targeting the

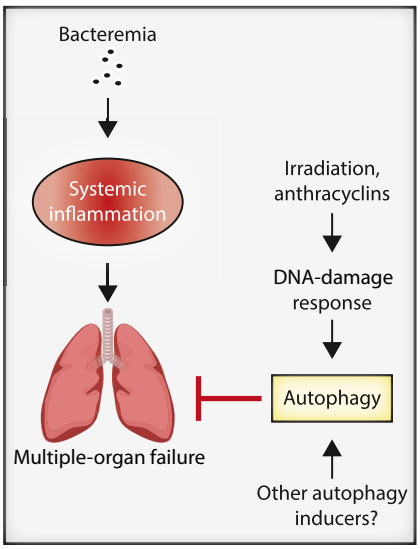

Figure 1. DNA-Damage-Activated Autophagy Protects from Septic Shock
Multiple-tissue failure during septic shock is caused by systemic inflammation. However, blocking inflammation once septic shock is diagnosed is inefficient for preventing mortality. Activation of autophagy by the DNA-damage response pathway in the lung has a powerful protective effect in a mouse model of sepsis. Whether other stimuli of autophagy activation are equally efficacious is not yet known.

pathogens (Ayres and Schneider, 2012; Medzhitov et al., 2012). When immunopathology or excessive inflammation are the main causes of morbidity and mortality, similar strategies operate by either suppressing the magnitude of the inflammatory response or reducing its negative impact on host tissues.

Whereas the distinct roles of resistance and tolerance are now increasingly well appreciated, the molecular mechanisms involved remain largely unknown. Using a short hairpin RNA (shRNA)-based screen, Figueiredo et al. identified three kinases involved in the DNA-damage response—the ATM (ataxia telangiectasia mutated), ATR (ataxia telangiectasia and Rad3 related), and CHEK1 (checkpoint kinase 1)—as mediators of the anti-inflammatory effects of anthracyclines in vitro. The authors next demonstrated that ATM is required in vivo for the protective effect of epirubicin in CLP-induced septic shock. Remarkably, activation of the DNA-damage response by sublethal γ irradiation was also sufficient to provide protection from mortality of CLP-induced sepsis. The authors next examined downstream targets of ATM and found that the autophagy pathway was required for the protective effect of epirubicin: in autophagy-defective *Lc3b*$^{-/-}$ mice the protection was lost. This led the authors to question which tissues required autophagy activation to provide protection from sepsis. Using inducible deletion of another autophagy gene, *Atg7*, in different cell types, Figueiredo et al. found that autophagy functioning specifically in the lung tissue was required for epirubicin-induced protection from septic shock.

This remarkable study has several important implications. First, the attempts to treat sepsis by targeting inflammatory pathways have been largely unsuccessful (Rittirsch et al., 2008). This is in part because by the time the septic shock is diagnosed, inflammation has already done a great deal of damage. Moreover, at the advanced stages of septic shock, when the patients become very sick, they generally enter the phase of disease characterized by immunosuppression (Rittirsch et al., 2008). The study by Figueiredo et al. illustrates that targeting the tissue tolerance to damage is a viable and perhaps the only efficacious therapeutic option. Similar evidence was obtained in another recent study demonstrating the role of tissue protection through heme detoxification in a CLP model of sepsis (Larsen et al., 2010). The second implication of the study by Figueiredo et al. is that mild challenge, such as treatment with DNA-damaging drugs or even γ irradiation, can result in lasting protective effects that can be life saving. This phenomenon, known as hormesis, has been particularly well documented with regard to defense against poisons and other toxic compounds, but it is applicable to any type of challenge (Kaiser, 2003). Indeed, the phenomenon of LPS tolerance is a relevant example of hormesis—low doses of lipopolysaccharide (LPS) afford complete protection from septic shock (Biswas and Lopez-Collazo, 2009). It is surprising that the relevant aspect of stress response identified by Figueiredo et al. as protective is the DNA-damage response and autophagy. One question raised by this finding is whether the DNA-damage pathway has a special role in the protection or whether any stimulus inducing autophagy is sufficient to prevent lethal tissue damage (Figure 1). Another key question for future studies is exactly how autophagy promotes tissue tolerance after inflammatory damage. Finally, the third important implication of this study is that it identifies the lung as the key target organ that required cytoprotection for the survival of the animals. Not all tissues and organs are equally important for survival—some are more vital than others. The tissues, organs, and physiological processes that have the lowest tolerance to damage and malfunction represent the weakest links in the body, and it is their damage or malfunction that ultimately kills. The weakest links are not necessarily the ones we can easily monitor or even be aware of—they are responsible for the proximal causes of death that are usually unknown. However, it is obvious that one can obtain the strongest therapeutic effects by targeting these potentially "rate-limiting" processes, such as respiration, cardiovascular and renal functions, and the function of the central nervous system. It would be important to determine whether tissue protection in the lung is also critical for survival in human patients.

In conclusion, the study by Figueiredo et al. opens up an important new chapter in the study and treatment of septic shock. It is likely to result in new developments and treatments for this deadly disease.

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